to 592 are from the Fc domain of human IgG1 (Lewis et al., J. Immunol. 151:2829-2838 (1993). (†) mark the two cysteines (amino acids number 371 and 374) of the IgG hinge preceding the Fc that form the inter-chain disulfide bridges that link two Fc domains. (•) shows the position of the STOP codon.

Please replace the paragraph starting on page 8, line 17, with the following:

FIGURES 9A-B (SEQ ID NO: 9). Amino acid sequence of gp130-Cγ1 (SEQ ID NO: 9). Key: Amino acids 1 to 619 are from human gp130 (Hibi, et al., Cell 63:1149-1157 (1990). Ser-Gly bridge is shown in bold type. Amino acids 662 to 651 are from the constant region of human IgG1 (Lewis et al., J. Immunol. 151:2829-2838 (1993). (*) shows the position of the STOP codon.

Please replace the paragraph starting on page 8, line 22, with the following:

FIGURE 10 (SEQ ID NO: 10). Amino acid sequence of gp130Δ3fibro (SEQ ID NO: 10). Key: Amino acids 1 to 330 are from human gp130 (Hibi et al., Cell 63:1149-1157 (1990). Other symbols as described in Figures 9A-9B (SEQ ID NO: 9).

Please replace the paragraph starting on page 8, line 26, with the following:

FIGURE 11 (SEQ ID NO: 11). Amino acid sequence of J-CH1 (SEQ ID NO: 11). Key: The Ser-Gly bridge is shown in bold, the J-peptide is shown in italics, the C_H1 domain is underlined.

Please replace the paragraph starting on page 9, line 1, with the following:

FIGURE 12 (SEQ ID NO: 12). Amino acid sequence of Cγ4 (SEQ ID NO: 12). Key: The Ser-Gly bridge is shown in bold type. Amino acids 2 to 239 comprise the Cγ4 sequence.

Please replace the paragraph starting on page 9, line4, with the following:

FIGURE 13 (SEQ ID NO: 13). Amino acid sequence of κ-domain (SEQ ID NO: 13). Key: The Ser-Gly bridge is shown in bold type. Amino acids 2 to 108 comprise the κ domain. The C-terminal cysteine (amino acid 108) is that involved in the disulfide bond of the κ domain with the CH1 domain of Cγ.

Please replace the paragraph starting on page 9, line 9, with the following:

FIGURE 14 (SEQ ID NO: 14). Amino acid sequence of λ-domain(SEQ ID NO: 14). Key: The Ser-Gly bridge is shown in bold type. Amino acids 2 to 106 comprise the λ domain (Cheung, et al., J. Virol. 66: 6714-6720 (1992). The C-terminal cysteine (amino acid 106) is that involved in the disulfide bond of the λ domain with the CH1 domain of Cγ.

Please replace the paragraph starting on page 9, line 15, with the following:

FIGURE 15 (SEQ ID NO: 15). Amino acid sequence of the soluble IL-6Rα domain (SEQ ID NO: 15). Key: Amino acids 1 to 358 comprise the soluble IL-6Rα domain (Yamasaki, et al., Science 241:825-828 (1988). The Ala-Gly bridge is shown in bold type.

Please replace the paragraph starting on page 9, line 19, with the following:

FIGURE 16 (SEQ ID NO: 16). Amino acid sequence of the soluble IL-6Rα313 domain (SEQ ID NO: 16): Key: Amino acids 1 to 313 comprise the truncated IL-6Rα domain (IL-6Rα313). The Thr-Gly bridge is shown in bold type.

Please replace the paragraph starting on page 10, line 11, with the following:

FIGURES 19A-19B. IL-6 can induce multimerization of the ligand trap. (Figure 19A) Two different ligand traps are depicted schematically and listed according to their ability to bind protein A. gp130-Fc•IL-6Rα-Fc (GF6F) binds protein A via its Fc-domains, whereas gp130-C_H1•IL-6Rα-k (G16K) does not bind to protein A. (Figure 19B) Anti-kappa western blotting of proteins precipitated with Protein A-Sepharose from mixtures of GF6F ± IL-6, G16K ± IL-6, or GF6F plus G16K ± IL-6, as marked.

Please replace the paragraph starting on page 11, line 1, with the following:

FIGURES 21A-21D (SEQ ID NOS: 17 and 18) - Nucleotide sequence (SEQ ID NO: 17) encoding and deduced amino acid sequence (SEQ ID NO: 18) of fusion polypeptide designated 424 which is capable of binding the cytokine IL-4 to form a nonfunctional complex.

Please replace the paragraph starting on page 11, line 5, with the following:

FIGURES 22A-22D (SEQ ID NOS: 19 and 20) - Nucleotide sequence (SEQ ID NO: 19) encoding and deduced amino acid sequence (SEQ ID NO: 20) of fusion polypeptide designated 603 which is capable of binding the cytokine IL-4 to form a nonfunctional complex.

Please replace the paragraph starting on page 11, line 9, with the following:

FIGURES 23A-23D (SEQ ID NOS: 21 and 22)- Nucleotide sequence (SEQ ID NO: 21) encoding and deduced amino acid sequence (SEQ ID NO:22) of fusion polypeptide designated 622 which is capable of binding the cytokine IL-4 to form a nonfunctional complex.

Please replace the paragraph starting on page 11, line 13, with the following:

FIGURES 24A-24F (SEQ ID NOS: 23 and 24) - Nucleotide sequence (SEQ ID NO: 23) encoding and deduced amino acid sequence (SEQ ID NO: 24) of fusion polypeptide designated 412 which is capable of binding the cytokine IL-6 to form a nonfunctional complex.

Please replace the paragraph starting on page 11, line 17, with the following:

FIGURES 25A-25F (SEQ ID NOS: 25 and 26) - Nucleotide sequence (SEQ ID NO: 25) encoding and deduced amino acid sequence (SEQ ID NO: 26) of fusion polypeptide designated 616 which is capable of binding the cytokine IL-6 to form a nonfunctional complex.

Please replace the paragraph starting on page 11, line 21, with the following:

FIGURES 26A-26E (SEQ ID NOS: 27 and 28)- Nucleotide sequence (SEQ ID NO: 27) encoding and deduced amino acid sequence (SEQ ID NO: 28) of fusion polypeptide designated 569 which is capable of binding the cytokine IL-1 to form a nonfunctional complex.

Please replace the paragraph starting on page 12, line 12, with the following:

FIGURES 31A-31G (SEQ ID NOS: 29 and 30) - The nucleotide (SEQ ID NO: 29) and encoded amino acid (SEQ ID NO: 30) sequence of the IL-4Rα.IL-13Rα1.Fc single chain trap construct is set forth.

Please replace the paragraph starting on page 12, line 15, with the following:

FIGURE 32A-32G (SEQ ID NOS: 31 and 32) - The nucleotide (SEQ ID NO: 31) and encoded amino acid sequence (SEQ ID NO: 32) of the IL-13Rα1.IL-4Rα.Fc single chain trap construct is set forth.

Please replace the paragraph starting on page 42, line 5, with the following:

SF21 insect cells obtained from *Spodoptera frugiperda* were grown at 27C in Gibco SF900 II medium to a density of $1x10^6$ cells/mL. The individual virus stock for either GP130-Fc-His_6 (Figures 4A and 4B [SEQ ID NO: 7]) or IL6Ra-Fc (Figure 5 [SEQ ID NO: 8]) was added to the bioreactor to a low multiplicity 0.01-0.1 PFU/cell to begin the infection. The infection process was allowed to continue for 5-7 days allowing maximum virus replication without incurring substantial cell lysis. The cell suspension was aseptically aliquoted into sterile

centrifuge bottles and the cells removed by centrifugation. The cell-free supernatant was collected in sterile bottles and stored at 4C until further use.

Please replace the paragraph starting on page 49, line 1, through page 51, line 13, with the following:

All the soluble receptor-Ig chimeric genes may be engineered in plasmid vectors including, but not limited to, vectors suitable for mammalian expression (Cos monkey kidney cells, Chinese Hamster Ovary cells [CHO], and ras-transformed fibroblasts [MG-ras]) and include a Kozak sequence (CGC CGC CAC CAT GGT G [SEQ ID NO: 3]) at the beginning of each chimeric gene for efficient translation. Engineering was performed using standard genetic engineering methodology. Each construct was verified by DNA sequencing, mammalian expression followed by western blotting with suitable antibodies, biophysical assays that determine ligand binding and dissociation, and by growth inhibition assays (XG-1, as described later). Since the domains utilized to engineer these chimeric proteins are flanked by appropriate restriction sites, it is possible to use these domains to engineer other chimeric proteins, including chimeras employing the extracellular domains of the receptors for factors such as IL-1, IL-2, IL-3, IL-4, IL-5, GM-CSF, LIF, IL-11, IL-15, IFNγ, TGFβ, and others. The amino acid coordinates for each component utilized in making the IL-6 traps are listed below (Note: numbering starts with the initiating methionine as #1; long sequences are listed using the single letter code for the twenty amino acids):

(a) Constructs employing human gp130:

(i) **gp130-Cγ1** was engineered by fusing in frame the extracellular domain of gp130 (amino acids 1 to 619) to a Ser-Gly bridge, followed by the 330 amino acids which comprise Cγ1 and a termination codon (Figures 9A and 9B [SEQ ID NO: 9]).

(ii) **gp130-J-Cγ1** was engineered in the same manner as gp130-Cγ1 except that a J-peptide (amino acid sequence: GQGTLVTVSS [SEQ ID NO: 4]) was inserted between the Ser-Gly bridge and the sequence of Cγ1 (see Figures 9A and 9B [SEQ ID NO: 9]).

(iii) **gp130Δ3fibro-Cγ1** was engineered by fusing in frame the extracellular domain of gp130 without its three fibronectin-like domains (Figure 10 [SEQ ID NO: 10]). The remaining part of this chimeric protein is identical to gp130-Cγ1.

(iv) **gp130-J-C_H1** was engineered in a manner identical for that described for gp130-Cγ1, except that in place of the Cγ1 region only the C_H1 part of Cγ1 has been used (Figure 11 [SEQ ID NO: 11]). The C-terminal domain of this construct includes the part of the hinge that contains the cysteine residue responsible for heterodimerization of the heavy chain of IgG with a light chain. The part of the hinge that contains the two cysteines involved in Cγ1 homodimerization has been deleted along with the C_H2 and C_H3 domains.

(v) **gp130-Cγ4** was engineered in a manner identical to that described for gp130-Cγ1, except that Cγ4 was used in place of Cγ1 (Figure 12 [SEQ ID NO: 12]). In addition, an *Rsr*II DNA restriction site was engineered at the hinge region of the Cγ4 domain by introducing two silent base mutations. The *Rsrs*II site allows for other desired genetic engineering manipulations, such as the construction of the C_H1 equivalent of gp130-Cγ4.

(vi) **gp130-κ** was engineered in a manner identical to that described for gp130-Cγ1, except that the constant region of the κ light chain of human Ig was used in place of Cγ1 (Figure 13 [SEQ ID NO: 13]).

(vi) **gp130-J-κ** was engineered in a manner identical to that described for gp130-J-κ, except that a j-peptide (amino acid sequence: TFGQGTKVEIK [SEQ ID NO: 5]) was inserted between the Ser-Gly bridge and the κ -region.

(viii) **gp130-λ** was engineered in a manner identical to that described for gp130-Cγ1, except that the constant region of the λ light chain (Cheung, et al., Journal of Virology 66:6714-6720 (1992) of human Ig was used in place of Cγ1 (Figure 14 [SEQ ID NO: 14]).

Constructs employing human IL-6Ra:

(i) **IL6R-Cγ1** was engineered by fusing in frame amino acids 1 to 358 of IL-6Rα (Yamasaki et al., Science 241:825-828 (1988), which comprise the extracellular domain of IL-6Rα (Figure 15 [SEQ ID NO: 15]), to an Ala-Gly bridge, followed by the 330 amino acids which comprise Cγ1 and a termination codon.

(ii) **IL6R-κ** was engineered as described for IL6R-Cγ1, except that the κ-domain (Figure 13 [SEQ ID NO: 13]) utilized for gp130-κ was used in place of Cγ1.

(iii) **IL6R-j-κ** was engineered as described for IL6R-κ except that the j-peptide described for gp130-j-κ was placed between the Ala-Gly bridge and the κ-domain.

(iv) Three additional constructs, **IL6R313-Cγ1**, **IL6R313-κ**, and **IL6R313-j-κ**, were engineered as using a truncated form of IL-6Ra comprised of amino acids 1 to 313 (Figure 16 [SEQ ID NO: 16]). Each of these constructs were made by fusing in frame IL6R313 with a Thr-Gly bridge followed by the Cγ1, κ-, and j-κ-domains described above. These constructs were engineered in order to complement the gp130Δ3fibro-derived constructs.

Please replace the paragraph starting on page 53, line 5, with the following:

In a different set of experiments the ability of the ligand traps to multimerize in the presence of ligand was tested. An example of this is shown on Figures 19A and 19B. IL-6-induced association of gp130-Fc•IL-6Rα-Fc with gp130-C_H1•IL-6Rα-κ was

determined by testing whether gp130-C_H1•IL-6Rα-κ, which does not by itself bind protein A, could be precipitated by protein A-Sepharose in the presence of gp130-Fc•IL-6Rα-Fc in an IL-6-depended manner (Figures 9A and 9B [SEQ ID NO: 9]). Precipitation of gp130-C_H1•IL-6Rα-κ by Protein A-Sepharose was determined by western blotting with an anti-kappa specific HRP conjugate, which does not detect gp130-Fc•IL-6Rα-Fc. gp130-C_H1•IL-6Rα-κ could be precipitated by Protein A-Sepharose only when both gp130-Fc•IL-6Rα-Fc and IL-6 were present. This result conclusively indicates that IL-6 can induce ligand trap multimerization, and further indicate that the ligand trap can mimic the hexameric cytokine•Rα•signal transducer complex (Figure 1). Ligand-induced multimerization may play a significant role in the clearance of cytokine•ligand trap complexes *in vivo*.

Please replace the paragraph starting on page 55, line 12, with the following:

The nucleotide sequences encoding the cytokine traps were constructed from the individual cloned DNAs (described *supra*) by standard cloning and PCR techniques. In each case, the sequences were constructed in frame such that the sequence encoding the first fusion polypeptide component was fused to the sequence encoding the second fusion polypeptide component followed by an Fc domain (hinge, CH2 and CH3 region of human IgG1) as the multimerizing component. In some cases extra nucleotides were inserted in frame between sequences encoding the first and second fusion polypeptide components to add a linker region between the two components (See Figures. 21A-21D [SEQ ID NO: 17] - trap 424; Figures. 24A-24F [SEQ ID NO: 23] - trap 412; and Figures. 26A-26E [SEQ ID NO: 27]- trap 569).

Please replace the paragraph starting on page 55, line 24, with the following:

For the IL-4 traps, 424 (Figures. 21A-21D [SEQ ID NO: 17]), 603 (Figures. 22A-22D [SEQ ID NO: 19]) and 622 (Figures. 23A-23D) [SEQ ID NO: 21], the IL-2Rγ component is 5', followed by the IL4Rα component and then the Fc component. For

the IL-6 traps, 412 (Figures. 24A-24F [SEQ ID NO: 23]) and 616 (Figures. 25A-25F [SEQ ID NO: 25]), the IL-6Rα component is 5' followed by the gp130 component and then the Fc domain. For the IL-1 trap 569 (Figures. 26A-26E [SEQ ID NO: 27] the IL-1RAcP component is 5' followed by the IL-1RI component and then the Fc domain. The final constructs were cloned into the mammalian expression vector pCDNA3.1 (STRATAGENE).

Please replace the paragraph starting on page 56, line 1, with the following:

In the 569 sequence (Figures. 26A-26E [SEQ ID NO: 27]), nucleotides 1-1074 encode the IL1RAcP component, nucleotides 1075 -1098 encode a linker region, nucleotides 1099-2043 encode the IL1RI component and nucleotides 2044-2730 encode the Fc domain.

Please replace the paragraph starting on page 56, line 7, with the following:

In the 412 sequence (Figures. 24A-24F [SEQ ID NO: 23]), nucleotides 1-993 encode the IL6Rα component, nucleotides 994-1023 encode a linker region, nucleotides 1024-2814 encode the gp130 component and nucleotides 2815-3504 encode the Fc domain.

Please replace the paragraph starting on page 56, line 12, with the following:

In the 616 sequence (Figures. 25A-25F [SEQ ID NO: 25]), nucleotides 1-993 encode the IL6Rα component, nucleotides 994-2784 encode the gp130 component and nucleotides 2785-3474 encode the Fc domain.

Please replace the paragraph starting on page 56, line 16, with the following:

In the 424 (Figures. 21A-21D [SEQ ID NO: 17]) and 622 (Figures. 23A-23D [SEQ ID NO: 21]) sequences, nucleotides 1-762 encode the IL2Rγ component, nucleotides 763-771 encode a linker region, nucleotides 772-1395 encode the IL4Rα component and nucleotides 1396-2082 encode the Fc domain.

Please replace the paragraph starting on page 56, line 21, with the following:

Finally, in the 603 sequence (Figures. 22A-22D [SEQ ID NO: 19]), nucleotides 1-762 encode the IL2Rγ component, nucleotides 763-1386 encode the IL4Rα component and nucleotides 1387-2073 encode the Fc domain.

Please replace the paragraph starting on page 62, line 11, with the following:

Figure 29 shows that the IL6 trap (6SC412 IL6R-scb-gpx-FcΔC1) described in Figures. 24A-24F (SEQ ID NOS: 23 and 24) is a better antagonist of IL-6 in the XG1 bioassay than the neutralizing monoclonal antibody to human IL-6 - BE8.

Please replace the paragraph starting on page 63, line 11, with the following:

Figure 30 shows that the trap 569 (Figures 26A - 26E [SEQ ID NOS: 27 and 28[) is able to antagonize the effects of IL-1 and block the IL-6 production from MRC 5 cells upon treatment with IL-1. At a concentration of 10nM, the trap 569 is able to block the production of IL-6 up to an IL-1 concentration of 3nM. In contrast, the IL-1RI.Fc is a much poorer antagonist of IL-1. It is only able to block the effects of IL-1 up to about 10-20 pM. Thus, the trap 569 is approximately 100x better at blocking IL-1 than IL1RI.Fc.

Please replace the paragraph starting on page 63, line 21, through 64, line 7, with the following:

1. To create the IL-13/IL-4 dual trap designated IL-4Rα.IL-13Rα1.Fc, the human IL-4Rα extracellular domain (corresponding to nucleotides #1-693 of Figures 31A - 31G [SEQ ID NO: 29]) and the human IL-13Rα1 extracellular domain (corresponding to nucleotides #700-1665 of Figures 31A - 31G [SEQ ID NO: 29]) were amplified by

standard PCR techniques and ligated into an expression vector pMT21 which contained the human Fc sequence (corresponding to nucleotides #1671-2355 of Figures 31A - 31G [SEQ ID NO: 29]), thus creating a fusion protein consisting of the IL-4Rα , IL-13Rα1, and the hinge, CH2 and CH3 region of human IgG1 from the N to C terminus. In addition, a two amino acid linker (corresponding to nucleotides #694-699 of Figures 31A - 31G [SEQ ID NO: 30]) with the amino acid sequence SerGly was constructed in frame between the IL-4Rα and the IL-13Rα1 and a two amino acid linker (corresponding to nucleotides #1666-1671 of Figures 31A - 31G [SEQ ID NO: 30]) with the amino acid sequence ThrGly was constructed in frame between the IL-13Rα1 and the Fc portion. All sequences were sequence-verified by standard techniques. The IL-4Rα.IL-13Rα1.Fc coding sequence was then subcloned into the expression vector pCDNA3.1 (Stratagene) using standard molecular biology techniques.

Please replace the paragraph starting on page 64, line 9, with the following:

2. To create the IL-13/IL-4 dual trap designated IL-13Rα1.IL-4Rα.Fc, the IL-13Rα1 extracellular domain (corresponding to nucleotides #1-1029 of Figure 32A - Figure 32G [SEQ ID NO: 31]) and the human IL-4Rα (corresponding to nucleotides # 1060-1692 of Figure 32A - Figure 32G [SEQ ID NO: 31]) were amplified by standard PCR techniques and ligated into the expression vector pJFE14, which contains the human Fc sequence (corresponding to nucleotides #1699-2382 of Figure 32A - Figure 32G [SEQ ID NO: 31]) to create a fusion protein consisting of the IL-13Rα1, IL-4Rα, and the hinge, CH2 and CH3 region of human IgG1 from the N to C terminus. In addition, a ten amino acid linker with the amino acid sequence GlyAlaProSerGlyGlyGlyGlyArgPro (SEQ ID NO: 6)(corresponding to nucleotide #1030-1059 of Figure 32A - Figure 32G [SEQ ID NO: 31]) was constructed in frame between the IL-13Rα1 and the IL-4Rα and a two amino acid linker (corresponding to nucleotides #1693-1698 of Figure 32A - Figure 32G [SEQ ID NO: 32]) with the amino acid sequence SerGly was constructed in frame between IL-4Rα and the Fc